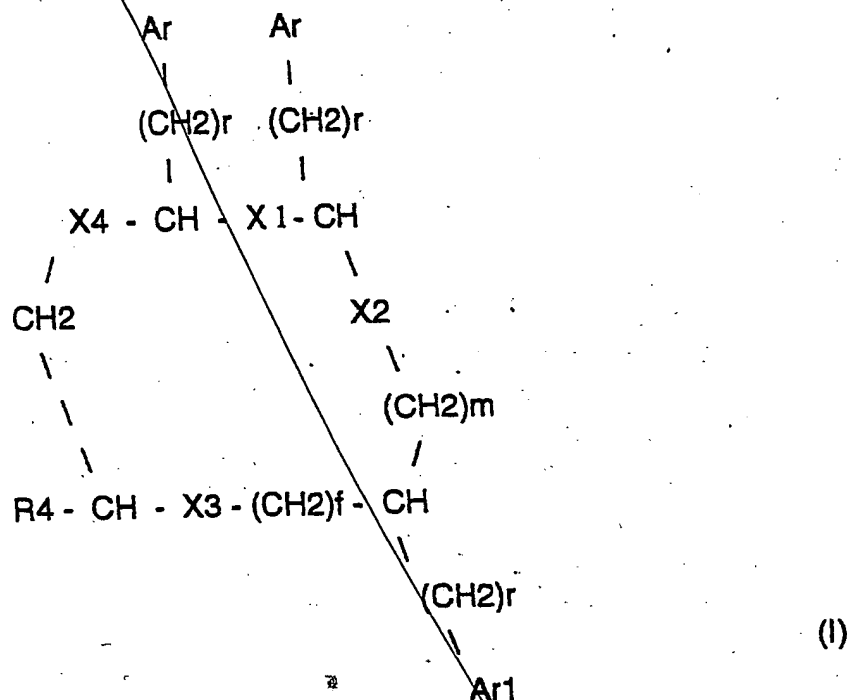


In the Claims

Please cancel claims 1-20, without prejudice or disclaimer.

Please add new claims 21-33, as follows:

--21. Monocyclic compounds of general formula (I)



wherein:

X₁, X₂, X₃, X₄ are the same or different, and are selected from the group consisting of -CONR-, -NRCO-, -CH₂-NR-, and -NR-CH₂- where R is selected from the group consisting of H, C₁₋₃ alkyl, and benzyl;

f, m, are the same or different, and is a number selected from the group consisting of 0, 1 and 2;

R₁ and R₂, are the same or different, and represent:

-(CH₂)_rAr where r is 0, 1 or 2 and Ar is an aromatic group selected from the group consisting of benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan,

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B benzofuran, thiazole, benzothiazole, imidazole, benzoimidazole, optionally substituted with up to 2 substituents selected from the group consisting of C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkyloxy, C₂₋₄ amino-alkyloxy, halogens, OH, NH₂, CN, and NR₆R₇, where R₆ and R₇, same or different, are H or C₁₋₃ alkyl,

Sub C1 R₃ is (CH₂)_rAr₁ where r is 0, 1 or 2 and Ar₁ is an aromatic group selected from the group consisting of benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, and benzimidazole,

optionally substituted with up to 2 groups selected from the groups consisting of C₁₋₃ alkyl and haloalkyl, C₁₋₃ alkyloxy and amino-alkyloxy, halogens, OH, NH₂, CN and NR₆R₇, where R₆ and R₇, same or different, are H or C₁₋₃ alkyl,

R₄ is NR₈R₉, where R₈ is H or C₁₋₃ alkyl; and

R₉ is selected from the group consisting of methanesulfonyl, tosyl, and tetrahydropyranyl, tetrahydrothiopyranyl optionally mono or di-substituted by oxygen on the S atom, piperidyl, optionally substituted on the N-atom by a C₁₋₃ alkyl, C₁₋₃ acyl, aminosulfonyl, or methanesulfonyl; or a group (CH₂)_gR₁₀ where g is 1, 2, or 3 and R₁₀ is selected from the group consisting of morpholine, furan and CN;

or R₈ and R₉ together with the N atom to which they are linked form a piperazine substituted on one of its nitrogens by a C₁₋₃ alkyl, C₁₋₃ acyl or methanesulfonyl;

-N(R₁₁)CO(CH₂)_hR₁₂ where R₁₁ is H or C₁₋₃ alkyl; h is 0, 1, 2 or 3; and R₁₂ is selected from the group consisting of morpholine, pyrrolidine optionally substituted with a hydroxy or hydroxymethyl, piperidine optionally substituted with a 4-hydroxy, 4-carboxyamido or 4-aminosulfonyl group, piperazine optionally substituted on the N-atom by C₁₋₃ alkyl, triazole, tetrazole, 5-mercapto-tetrazole, furan, thiophene, thiomorpholine, optionally mono or di-oxygenated on the S-atom, and amino- cyclohexane optionally substituted on a hydroxy group;

- COR₁₃ wherein R₁₃ is a member selected from the group consisting of morpholine and piperazine optionally substituted by a C₂₋₆ alkyl containing one or more ether or hydroxy groups; their enantiomers and mixtures thereof, their diastereoisomers, and their pharmaceutically acceptable salts.

22. Compound according to Claim 21 wherein:

f is 1

m is 0

B
Sub
Cl
 X_1, X_2, X_3, X_4 are the same or different and are a member selected from the group consisting of -CONR- and -NRCO-,

where R is H or methyl,

R_1 and R_2 are the same or different, are:

-CH₂Ar wherein Ar is an aromatic group selected from the group consisting of benzene, pyridine, indole, optionally substituted with up to two residues with substituents selected from the group consisting of C₁₋₃ alkyl and haloalkyl, C₁₋₃ alkyloxy, C₂₋₄ amino alkyloxy, halogens, OH, NH₂, CN, and NR₆R₇, where R₆ and R₇, same or different, and are H or C₁₋₃ alkyl;

R_3 is -CH₂Ar₁ wherein Ar₁ is an aromatic group selected from the group consisting of alpha naphthyl, beta naphthyl, phenyl, phenyl substituted with up to two residues selected from the group consisting of C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkyloxy, halogens, OH, and NH₂.

23. Compounds according to Claim 22 wherein:

- X_1, X_2, X_3, X_4 are -CONH-,

- R_1 is indol-3-yl-methyl

- R_2 is phenyl-methyl optionally substituted with up to two residues selected from the group consisting of chlorine, fluorine, CF₃, OH, CN, 3-pyridyl-methyl and 4-pyridyl-methyl;

- R_3 is benzyl.

24. Compounds according to claim 23 wherein:

R_4 is a group NR₈R₉ wherein:

R_8 is H or methyl;

R_9 selected from the group consisting of 4-tetrahydropyranyl, 4-tetrahydrothiopyranyl, 1-oxo-tetrahydrothiopyran-4-yl, 1,1-dioxo-tetrahydrothiopyran-4-yl, N-methyl-4-piperidinyl, N-methanesulfonyl-4-piperidinyl, and N-aminosulfonyl-4-piperidinyl,

or R₈ and R₉ together with the N atom to which they are linked represent N-methyl-piperazinyl, N-acetyl-piperazinyl or N-methanesulfonyl-piperazinyl.

25. Compounds according to Claim 24 represented by:

- Sub C2
- i) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
 - ii) cyclo{Suc[1-(S)-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
 - iii) cyclo{Suc[1-(R)-(1-methyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
 - iv) cyclo{Suc[1-(R)-(4-tetrahydrothiopyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
 - v) cyclo{Suc[1-(R)-(1-oxo-tetrahydrothiopyran-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
 - vi) cyclo{Suc[1-(R)-(1,1-dioxo-tetrahydrothiopyran-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
 - vii) cyclo{Suc[1-(R)-N-methyl-N-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
 - viii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Tyr-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
 - ix) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-F)-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
 - x) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(3,5-F)-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
 - xi) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-CN)-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
 - xii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-CF₃)-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
 - xiii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Ala(4-pyridyl)-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
 - xiv) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Ala(3-pyridyl)-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}

Sub C2
xv) cyclo{Suc[1-(R)-(1-methylsulfonyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}

xvi) cyclo{Suc[1-(R)-(1-aminosulfonyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}

xvii) cyclo{Suc[1-(R)-4-methyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}

xviii) cyclo{Suc[1-(R)-4-acetyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]} or

xix) cyclo{Suc[1-(R)-4-methylsulfonyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}.

26. Compounds according to Claim 23 wherein :

R₄ represents a group NR₈R₉, where R₈ is H and R₉ is methanesulfonyl, tosyl or a group (CH₂)_gR₁₀, wherein g is 1 or 2 and R₁₀ is morpholine, furan, or CN.

27. Compounds according to claim 26 represented by:

xx) cyclo{Suc[1-(S)-4-methylsulfonylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}

xxi) cyclo{Suc[1-(R)-4-methylsulfonylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}

xxii) cyclo{Suc[1-(S)-(4-methylphenyl)sulfonylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}

xxiii) cyclo{Suc[1-(R)-(4-methylphenyl)sulfonylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}

xxiv) cyclo{Suc[1-(S)-2-(4-morpholino)ethylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}

xxv) cyclo{Suc[1-(R)-2-(4-morpholino)ethylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}

xxvi) cyclo{Suc[1-(R)-(2-furyl)methylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]} or

xxvii) cyclo{Suc[1-(R)-cyanomethylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}.

28. Compounds according to claim 23 wherein:

R₄ is a group - N(R₁₁)CO(CH₂)_h-R₁₂ wherein R₁₁ is H, h is 0 or 1, and R₁₂ is selected from the group consisting of 1-tetrazolyl, 5-mercapto-tetrazol-1-yl, 1-triazolyl, furanyl, thiophenyl, morpholine, 4-hydroxy-piperidine, 4-carboxyamido-piperidine, 3-hydroxy-pyrrolidine, 2-hydroxymethylpyrrolidine, 4-methyl-piperazine, 4-aminosulfonyl-piperazine, 1-oxo-

thiomorpholine, and 4-hydroxy-cyclohexan-1-yl-amino.

29. Compounds according to Claim 28 represented by:

- xxviii) cyclo{Suc[1-(R)-2-(4-morpholino)acetylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
- xxix) cyclo{Suc[1-(S)-2-(4-morpholino)acetylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
- xxx) cyclo{Suc[1-(S)-2-(tetrazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
- xxxi) cyclo{Suc[1-(R)-2-(tetrazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
- xxxii) cyclo{Suc[1-(S)-2-(5-mercapto-tetrazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
- xxxiii) cyclo{Suc[1-(R)-2-([1,2,4]triazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
- xxxiv) cyclo{Suc[1-(R)-2-(furanyl)carbonylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
- xxxv) cyclo{Suc[1-(R)-2-(thiophen-3-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
- xxxvi) cyclo{Suc[1-(R)-2-(4-morpholino)carbonylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
- xxxvii) cyclo{Suc[1-(R)-2-(4-hydroxy-piperidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
- xxxviii) cyclo{Suc[1-(R)-2-(4-aminocarbonyl-piperidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
- xxxix) cyclo{Suc[1-(R)-2-(3-hydroxy-pyrrolidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
- xl) cyclo{Suc[1-(R)-2-(2-(S)-hydroxymethyl-pyrrolidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
- xli) cyclo{Suc[1-(R)-2-(4-methyl-piperazin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}
- xl ii) cyclo{Suc[1-(R)-2-(4-methyl-piperazin-1-yl)carbonylamino]-Trp-Phe-[(R)-NH-CH(CH₂-

C₆H₅)-CH₂NH]}}

xliv) cyclo{Suc[1-(R)-2-(4-aminosulfonyl-piperazin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}}

xliv) cyclo{Suc[1-(R)-2-(1-oxo-thiomorpholin-4-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}} or

xliv) cyclo{Suc[1-(R)-2-(*trans*-4-hydroxy-cyclohexan-1-yl-amino)acetylamino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}}.

30. Compounds according to Claim 23 wherein:

R₄ represents a group COR₁₃ wherein R₁₃ is a member selected from the group consisting of morpholine and 4-(hydroxyethyloxyethyl)-piperazine.

31. Compounds according to claim 30 represented by:

xlvi) cyclo{Suc[1-(4-morpholino)carbonyl]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}} or

xlvi) cyclo{Suc[1-(4-hydroxyethyloxyethyl-piperazin-1-yl)carbonyl]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂NH]}}.

32. Pharmaceutical compositions containing as active principle compounds of general formula (I) according to Claim 21 in combination with pharmaceutically acceptable carriers or excipients.

33. A method for the treatment of the bronchospastic component of asthma, cough, pulmonary irritation, intestinal spasms or local spasms of bladder, ureters during cystitis, kidney infections and colics wherein amounts of 0.1 to 10mg/kg body weight of an active principle represented by compounds of formula (I) according to Claim 21 are administered to the patient.

REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments and the remarks which follow. Applicants have endeavored to address each of the issues raised by the Examiner and, by so doing, to advance the prosecution of the application to allowance.

Applicants have cancelled claims 2-15, 19 and 20 without prejudice or disclaimer, and have added new claims 21-33 inclusive all of which are fully supported in the as-filed